## **CENTER FOR DRUG EVALUATION AND** RESEARCH

**APPLICATION NUMBER: NDA 20-757/S-014** 

**APPROVAL LETTER** 



Food and Drug Administration Rockville MD 20857

NDA 20-757/S-014

5/26/01

Bristol-Myers Squibb Attention: Ms. Grace Heckman P.O. Box 4000 Princeton, NJ 08543-4000

Dear Ms. Heckman:

Please refer to your supplemental new drug application dated February 16, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets.

We acknowledge receipt of your submission dated April 25, 2001 that constituted a complete response to our December 15, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. Under CLINICAL PHARMACOLOGY, the Special Populations, the *Pediatric* subsection has been changed to:

The pharmacokinetics of irbesartan were studied in hypertensive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following single and multiple daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and Cmax values were comparable to adults receiving 150 mg daily. Irbesartan pharmacokinetics have not been investigated in patients <6 years of age.

2. Under PRECAUTIONS, Pediatric Use, a second paragraph has been added that reads:

Pharmacokinetic parameters in pediatric subjects (age 6–16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (see CLINICAL PHARMACOLOGY; Special Populations). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (See DOSAGE and ADMININSTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

3. Under DOSAGE and ADMINISTRATION, a Pediatric Patients subsection has been added:

Children (< 6 years): safety and effectiveness have not been established.

Children (6-12 years): An initial dose of 75 mg once daily is reasonable. Patients requiring further reduction in blood pressure should be titrated to 150 mg once daily (see PRECAUTIONS; Pediatric Use).

Adolescent patients (13-16 years): An initial dose of 150 mg once daily is reasonable. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see PRECAUTIONS; Pediatric Use).

4. Under HOW SUPPLIED, the 75 mg Blister Pack of 100 (NDC# 0087-2771-35) has been removed.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submission of April 25, 2001). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm Regulatory Health Project Manager (301) 594-5313

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.

Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: NDA 20-757/S-014** 

## APPROVABLE LETTER

NDA 20-757 Page 1

NDA 20-757/S-014

Bristol-Myers Squibb
Pharmaceutical Research Institute
Attention: Ms. Grace Heckman
P.O. Box 4000
Princeton, NJ 08543-4000

### Dear Ms. Heckman:

Please refer to your supplemental new drug application (NDA) dated February 16, 2000, received February 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75, 150, and 300 mg.

This supplemental new drug application proposes changes in the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE and ADMINISTRATION sections of the labeling.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. The CLINICAL PHARMACOLOGY, Special Populations, Pediatric subsection should read as follows:

The pharmacokinetics of irbesartan were studied in hypertensive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following acute and repeated daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and Cmax values were comparable to adults receiving 150 mg daily. Irbesartan pharmacokinetics have not been investigated in patients <6 years of age.

2. The PRECAUTIONS, Pediatric Use subsection should read as follows:

Safety and effectiveness in pediatric patients have not been established.

Pharmacokinetic parameters in pediatric subjects were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (age 6-16; n=21). (see CLINICAL PHARMACOLOGY; Special Populations). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (See DOSAGE and ADMININSTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

3. The DOSAGE and ADMINISTRATION, Pediatric Patients subsection should read as follows:

Children (< 6 years): safety and effectiveness have not been established.

Children (6-12 years): An initial dose of 75 mg once daily is recommended. Patients requiring further

reduction in blood pressure should be titrated to 150 mg once daily. (see PRECAUTIONS; Pediatric Use).

Adolescent patients (13-16 years): An initial dose of 150 mg once daily is recommended. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see PRECAUTIONS; Pediatric Use).

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Edward Fromm Regulatory Health Project Manager (301) 594-5313

Sincerely,

**/S/** 

Raymond J. Lipicky, M.D.

Director

Division of Cardio-Renal Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

APPROVABLE (AE)

Letter #1 see

NDA 20-757 Page 1

NDA 20-757

Bristol-Myers Squibb Pharmaceutical Research Institute Attention: Ms. Grace Heckman P.O. Box 4000 Princeton, NJ 08543-4000

### Dear Ms. Heckman:

Please refer to your new drug application (NDA) dated February 16, 2000, received February 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75, 150, and 300 mg.

This supplemental new drug application proposes changes in the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE and ADMINISTRATION sections of the labeling.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. The CLINICAL PHARMACOLOGY, Special Populations, Pediatric subsection should read as follows:

The pharmacokinetics of irbesartan were studied in hypertensive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following single and multiple daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and Cmax values were comparable to adults receiving 150 mg daily. Irbesartan pharmacokinetics have not been investigated in patients <6 years of age.

2. The PRECAUTIONS, Pediatric Use subsection should read as follows:

Safety and effectiveness in pediatric patients have not been established.

Pharmacokinetic parameters in pediatric patients (age 6-16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (see CLINICAL PHARMACOLOGY; Special Populations). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (See DOSAGE and ADMININSTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

3. The DOSAGE and ADMINISTRATION, Pediatric Patients subsection should read as follows:

Children (< 6 years): safety and effectiveness have not been established.

reasonable

Children (6-12 years): An initial dose of 75 mg once daily is recommended. Patients requiring further reduction in blood pressure should be titrated to 150 mg once daily. (see **PRECAUTIONS**; Pediatric Use).

Adolescent patients (13-16 years): An initial dose of 150 mg once daily is recommended. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see PRECAUTIONS; Pediatric Use).

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Edward Fromm Regulatory Health Project Manager (301) 594-5313

Sincerely,

Raymond J. Lipicky, M.D.

Director

Division of Cardio-Renal Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

cc:

Archival NDA 20-757 HFD-110/Div. Files HFD-110/E.Fromm

## Corrections to the December 15, 2000 approvable letter for Avapro (irbesartan ) Tablets NDA 20-757 (S-014)

Dear Ms. Heckman:

Please note the following changes in regard to the approvable letter issued December 15, 2000 for Avapro (irbesartan) Tablets, 75, 150, and 300 mg.

Under DOSAGE and ADMINISTRATION, Pediatric Patients subsection, the word "reasonable" should replace "in the first sentence of the "Children (6-12 years) and Adolescent patients (13-16 years) subheadings.

Please make note of the above corrections before sending in final printed labeling.

Thank you,

/\$/

Edward Fromm Regulatory Health Project Manager (301) 594-5313

## Note on Approvable letter sent by Fax on December 18, 2000 for NDA 20-757,(S-014) Avapro (irbesartan) Tablets, 75, 150, and 300 mg

Dear Ms. Heckman:

Please note that the December 18, 2000 faxed approvable letter (with Dr. Lipicky's handwritten signature) supersedes the electronic version dated December 15, 2000 signed by Dr. Throckmorton (for Dr. Lipicky).

Please also note the following specific differences between the two letters:

- 1) Under DOSAGE and ADMINISTRATION, Pediatric Patients subsection, the word "reasonable" should replace

  2 in the first sentence of the "Children (6-12 years) and Adolescent patients (13-16 years) sections.
- 2) Under CLINICAL PHARMACOLOGY, Special Populations, Pediatric subsection, the phrase "single and multiple" daily doses... should replace "daily doses... in the first sentence of this subsection.
- 3) Under PRECAUTIONS, Pediatric Use subsection, the second sentence should read "Pharmacokinetic parameters in pediatric patients (age 6-16, n=21) were comparable to adults."

Please make note of the above differences before sending in final printed labeling.

I apologize for any confusion the differences in the two letters may have caused.

Thank you,

15/ 2/1/01

Edward Fromm Regulatory Health Project Manager (301) 594-5313

## **CENTER FOR DRUG EVALUATION AND** RESEARCH

**APPLICATION NUMBER: NDA 20-757/S-014** 

## FINAL PRINTED LABELING

p it

CI

Si Pi 80 11

11

6

irt

alı ye thi mi iS als DC

10 ne

Ph In

do:

800

tan

ren

ser

filtr

the

fasi

tion

Cilr

The

8-1

ma

stuc trou

troll

in c

sart

vide

(24

8-1

The

ŤI

le

MAY 2 6 2001

# **AVAPRO**® (irbesartan) Tablets



1017101A5 AVAPRO® (Irbesartan) Tablets

### **USE IN PREGNANCY**

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVAPRO should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

### DESCRIPTION

AVAPRO® (Irbesartan) is an anglotensin il receptor (AT, subtype) antagonist.

irbesartan is a non-peptide compound, chemically described as a 2-bulyi-3-[[2'-(1 M-tetrazol-5-yl) [1, 1'-biphenyi]-4-yi]methyi]-1,3-diazaspiro [4,4] non-1-en-4-one.

Its empirical formula is C<sub>25</sub>H<sub>28</sub>N<sub>6</sub>O, and the structural formula:

Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

AVAPRO is available for oral administration in unacored tablets containing 75 mg, 150 mg, or 300 mg of irbesartan, inactive ingredients include: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide and magnesium stearate.

### **CLINICAL PHARMACOLOGY**

### Mechanism of Action

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and amouth muscle cell growth. Irbesertan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT, angiotensin if receptor. There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

irbesartan is a specific competitive antagonist of AT<sub>1</sub> receptors with a much greater affinity (more than 8500-fold) for the  $AT_1$  receptor than for the  $AT_2$  receptor and no agonist activity.

Blockade of the AT<sub>1</sub> receptor removes the negative feedback of anglotensin (i on renin secretion, but the resulting increased plasma renin activity and circulating anglotensin II do not overcome the effects of irbesartan on blood pressure.

irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical refevance is not known.

### **Pharmacokinetics**

irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesertan is rapid and complete with an average absolute bioevaliability of 60-80%. Following oral administration of AVAPRO, peak plasma concentrations of incesartan are attained at 1.5-2 hours after dosing. Food does not affect the bioavailability of AVAPRO.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesertan averaged 11-15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

### Metabolism and Elimination

irbesertan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of MC-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesertan. The primary circulating metabolite is the inactive irbesertan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to Irbesartan's pharmacologic activity.

irbesartan and its metabolites are excreted by both billiary and renal routes. Following either oral or intravenous administration of <sup>14</sup>C-labeled irbesertan, about 20% of radioactivity is recovered in the uring and the remainder in the faces, as irbesertan or irbesertan glucuronide.

In vitre studies of irbesartan exidation by cytochrome P450 lecenzymes indicated irbesartan was exidized primarily by 2C9; metabolism by 3A4 was negligible, irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1. 1A2, 2A5, 2B5, 2D6, 2E1). There was no induction or inhibition of SA4.

Irbesartan is 90% bound to serum proteins (primarily albumin and  $\alpha_1$ -acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53-93 liters. Total

\*Registered trademark of Sanofi-Synthelabo

plasme and renal clearances are in the range of 157-176 and 3.0-3.5 mL/min, respectively. With regettive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weakly crosses the blood brain barrier and placenta. Irbesertan is excreted in the milk of lactating rate.

### Special Populations

Pediatric: The pharmacokinetics of irbesartan were studied in hypertanaive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following single and multiple daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and C<sub>max</sub> values were comparable to adults receiving 150 mg daily. Inbesartan pharmacokinetics have not been investigated in patients <6 years of age.

Gender: No gender related differences in pharmacokinatics were observed in healthy elderly (age

65-80 years) or in healthy young (age 18-40 years) subjects. In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but somewhat higher plasma concentrations of irbesartan were observed in females (11-44%). No gender-related dosage adjustment is necessary.

Geriatric: in elderly subjects (age 65-80 years), irbesartan elimination half-life was not significantly

attered, but AUC and C<sub>max</sub> values were about 20-50% greater than those of young subjects (age 18-40 years). No desage adjustment is necessary in the alderly.

Race: In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites;

there were no differences in Cmex values.

Renal insufficiency: The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesertan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted. (See WARNINGS: Hypotension in Volume- or Sait-depleted Patients and DOSAGE AND ADMINISTRATION

Hepatic insufficiency: The pharmacokinatics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug Interactions: (See PRECAUTIONS: Drug Interactions.)

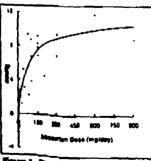
In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of anglotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin il receptor inhibition following chronic administration of irbesertan causes a 1.5-2 fold rise in angiotensin il plasma concentration and a 2-3 fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses.

in hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration, and no uricosuric effect.

The antihypertensive effects of AVAPRO (irbesartan) were examined in seven (7) major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressures of 95-110 mmHg. Doses of 1-900 mg were included in these trials in order to fully explore the dose-range of irbesertan. These studies allowed comparison of once- or twice-daily regimens at 150 mg/day, comparisons of peak and trough effects, and comperisons of response by gender, age, and race. Two of the seven placebo-controlled trials identified above examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination

The seven (7) studies of Irbesartan monotherapy included a total of 1915 patients randomized to irbesartan (1-900 mg) and 611 patients randomized to placebo. Once-daily doses of 150 and 300 mg provided statistically and clinically significant decreases in systolic and disabilic blood pressure with trough (24 hours post-dose) effects after 6-12 weeks of treatment compared to placebo, of about 8-10/5-6 and 8-12/5-8 mmHg, respectively. No further increase in effect was seen at desages greater than 300 mg. The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 1 and 2.



yn 9. Pissebs-subtracted reduction in yn Besan; integrated analysis

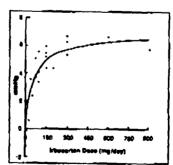


Figure 2. Pisceba-subtracted reduction in

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3-6 hours and, in one ambulatory blood pressure monitoring study, again around 14 hours. This was seen with both once-daily and twice-daily dosing. Trough-to-peak ratios for systolic and diastolic response were generilly between 60-70%. In a continuous ambulatory blood pressure monitoring study, once-daily dealing with 150 mg gave trough and mean 24-hour responses similar to those observed in patients receiving twice-daily dosing at the same total daily dose.

In controlled trials, the addition of irbevarian to hydrochlorothlazide doses of 6.25, 12.5, or 25 mg produced further dose-related reductions in blood pressure similar to those achieved with the same

monotherapy dose of irbesartan. MCTZ also had an approximately additive effect.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses. Irbesartan was effective in reducing blood pressure regardless of race, although the offect was somewhat less in blacks (usually a low-renin population).

The effect of Irbasertan is apparent after the first dose and it is close to its full observed affect at 2 weeks. At the end of an 8-week exposure, about 2/3 of the antihypertensive effect was still present one week after the last dose. Rebound hypertension was not observed. There was essentially no change in average heart rate in irbasartan-treated patients in controlled trials.

### INDICATIONS AND USAGE

AVAPRO (irbesartan) is Indicated for the treatment of hypertension, it may be used alone or in combination with other antihypertensive agents.

### **CONTRAINDICATIONS**

AVAPRO is contraindicated in patients who are hypersensitive to any component of this product.

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-anglotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature In patients who were taking angiotensin-converting-enzyme inhibitors. When pregnancy is detected, AVAPRO should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and recinatal injury, including hypotension, neonatal skull hypoplasia, anuna, reversible or irreversible renal failure, and death. Oligohydrampios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnics in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductua arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin il receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of AVAPRO as soon as possible.

Rarely (probably less often then once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the Intraamniotic environment.

If oligohydramnios is observed, AVAPRO should be discontinued unless it is considered life-saving for the mother. Contraction stress teating (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnics may not appear until after the fetus has sustained irreversible injury.

infants with histories of in utero exposure to an anglotensin il receptor entagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal pertusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with inbesartan from day 0 to day 20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal polvic cavitation, hydroureter and/or absence of ranal papilia were observed in fetuses at doses ≥50 mg/kg/day [approximately equivalent to the maximum recommended human dose (MRHD), 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses ≥180 mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anomalies were not observed in rats in which inbesartan exposure (oral doses of 50, 150 and 450 mg/kg/day) was limited to gestation days 6-15, they appear to reflect late gestational affects of the drug. In pregnant rabbits, oral doses of 30 mg irbesertan/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early resorptions and a corresponding decrease in live fetuses. Irbesertan was found to cross the placental barrier in rate and rabbits.

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

Hypotension in Volume- or Salt-depleted Patients
Excassive reduction of blood pressure was rarely seen (<0.1%) in patients with uncomplicated hypertension. Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or eodium-depletion, e.g., in patients treated vigorously with diuretice or in patients on dialysis. Such volume depletion should be corrected prior to administration of AVAPRO, or a low starting dose should be used (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

### **PRECAUTIONS**

### **Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart fall-ure), treatment with angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azoternia and (rarely) with acute renal failure and/or death. AVAPRO would be expected to behave similarly. In studies of ACE inhibitors in patients with unlisteral or bilateral renai artary stendals, increases in serum creatinine or BUN have been reported. There has been no known use of AVAPRO in patients with unitateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

### Information for Patients

Prepnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intravterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians ea soon as possible.

### Drug Interactions

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in Interaction studies with hydrochlorothlazide, digoxin, warfarin, and nifedipline.

in vitro studies show algoriticant inhibition of the formation of oxidized inbesarten metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulphenazole, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant inbesartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes 1A1, 1A2, 2A8, 2B6, 2D6, 2E1, or 3A4.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesarten administration for 7 days had no effect on the pharmacodynamics of warferin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine or hydrochlorothiazide.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rate and 1000 mg/kg/day in mice for up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC<sub>D-24h</sub>, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humana receiving the meximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to Irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of in vitro tests (Ames' microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (In vitro-human lymphocyte assay; In vivo-mouse micronucleus study).

irbesartan had no adverse effects on fertility or mating of male or female rate at oral doses ≤650 mg/kg/day, the highest dose providing a systemic exposure to irbesertan (AUC<sub>0-24h</sub>, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

### Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimester).

See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Methers
It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Pharmacokinetic parameters in pediatric subjects (age 6-16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irresertan) was well tolerated in hypertensive children and adolescents (see CLINICAL PHARMACOLOGY: Special Populations). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients can-not be ruled out (see DOSAGE AND ADMINISTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

Of the total number of patients receiving AWAPRO (irbesartan) in controlled clinical studies, 911 patients (18.5%) were 65 years and over, while 150 patients (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but preater sensitivity of some older individuals cannot be ruled out.

### **ADVERSE REACTIONS**

AVAPRO has been evaluated for safety in more than 4300 patients with hypertension and about 5000 subjects overall. This experience includes 1303 patients treated for over 6 months and 407 patients for 1 year or more. Treatment with AVAPRO was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of AVAPRO.

in placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3 percent of patients treated with AVAPRO, versus 4.5 percent of patients given placebo.

In placebo-controlled clinical trials, the adverse event experiences that occurred in at least 1% of patients treated with AVAPRO (n=1965) and at a higher incidence versus placebo (n=641) included diarrnee (3% vs. 2%), dyspepsia/heartburn (2% vs. 1%), musculoekeletal trauma (2% ys. 1%), fatigue (4% vs. 3%), and upper respiratory infection (9% vs. 6%). None of these differences were significant.

The following adverse events occurred at an incidence of 1% or greater in patients treated with Irbesartan, but were at least as frequent or more frequent in patients receiving placebo: abdominal pain. anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculosketetal pain, pharyngitis, nausea/vomiting, rash, rhinitis, sinus abnormality, tachycardia and urinary tract infection.

Irbesartan use was not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitor use. In placebo controlled studies, the incidence of cough in irbesartan treated patients was 2.8% versus 2.7% in patients receiving piacebo.

The incidence of hypotension or orthostatic hypotension was low in irbesartan treated patients (0.4%). unrelated to dosage, and similar to the incidence among placebo treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving irresertan compared with placebo.

in addition, the following potentially important events occurred in less than 1% of the 1965 patients and at least 5 patients (0.3%) receiving tresertan in clinical studies, and those less frequent, clinically significant events (listed by body system). It cannot be determined whether these events were causally related to irbeserten:

Body as a Whole: fever, chills, facial edema, upper extremity edema;

Cardiovascular: flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoria, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis;

Dermatologic: pruritus, dermatitis, ecchymosis, erythoma face, urticaria;

Endocrine/Matabolic/Electrolyte Imbalances: sexual dysfunction, libido change, gout;

Gastrointestinal: constipation, oral lesion, gastroenteritis, flatulence, abdominal distention;

Musculoskeletal/Connective Tissue: extremity swelling, muscle cramp, arthritis, muscle ache, muscuigakeletal chest pain, joint stiffness, bursitis, muscle weakness;

Nervous System: eleep disturbance, numbness, somnolence, emotional disturbance, depression, paresthesia, fremor, transient ischemic attack, cerebrovascular accident;

Renal/Genitourinary: abnormal urination, prostate disorder:

Respiratory: epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyapnes, wheezing; Special Senses: vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis, other eye disturbance, eyelid abnormality, ear abnormality.

Post-Marketing Experience

The following have been very rarely reported in post-marketing experience: urticarie; angloedems (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; laundica. Hyperkalemia has been rarely reported.

**Laboratory Test Findings** 

In controlled clinical triefs, clinically important differences in laboratory tasts were rarely associated with administration of AVAPRO.

Creatinine, Bipod Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with AVAPRO alone versus 0.9% on placabo. (See PRECAUTIONS: Impaired Renal Function.)

Hematologic: Mean decreases in hemoglobin of 0.2 g/di, were observed in 0.2% of patients receiving AVAPRO compared to 0.3% of placebo treated patients. Neutropenia (<1000 celts/mm3) occurred at elmliar frequencies among patients receiving AVAPRO (0.3%) and placebo treated patients (0.5%).

No date are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poleon-Control Center. Telephone numbers of certified polson-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

Laboratory determinations of serum levels of irbesertan are not widely available, and such determinations have, in any event, no known established role in the management of irbesertan overdose.

Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg) on a mg/m² basis, respectively.

### DOSAGE AND ADMINISTRATION

The recommended initial dose of AVAPRO (Irresertan) is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A low dose of a diuretic may be added, if blood pressure is not controlled by AVAPRO alone. Hydrochlorothlexide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY: Clinical Studies). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

No dosage adjustment is necessary in elderly patients, or in patients with hepatic impairment or mild to severe renal impairment.

AVAPRO may be administered with other antihypertensive agents. AVAPRO may be administered with or without food.

### Pediatric Patients

Children (<6 years): Safety and effectiveness have not been established.
Children (6-12 years): An initial dose of 75 mg once daily is reasonable. Patients requiring further reduction in blood pressure should be titrated to 150 mg once daily (see PRECAUTIONS: Pediatric Use).

Adolescent patients (13-16 years): An initial does of 150 mg once dally is resemble. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see PRECAUTIONS: Pediatric Use).

Volume- and Salt-degleted Patients
A lower initial dose of AVAPRO (75 mg) is recommended in patients with depletion of intravascular volume. ume or salt (e.g., patients treated vigorously with diuretics or on hemodialysis) (see WARNINGS: Hypotensien in Volume- or Sait-depleted Patients).

### HOW SUPPLIED

AVAPRO® (Irbesartan) is available as white to off-white biconvex oval tablets, debossed with a heart shape on one side and a portion of the NDC code on the other. Unit-of-use bottles contain 30, 90, or 500 tablets and blister packs contain 100 tablets, as follows:

	75 mg	150 mg	300 mg
Debossing	2771	2772	2773
Bottle of 30	0087-2771-31	0087-2772-31	0087-2773-31
Battle of 90	0087-2771-32	0087-2772-32	0087-2773-32
Bottle of 500		0087-2772-15	0087-2773-15
Blister of 100		0087-2772-35	

### Storage

Store at a temperature between 15° C and 30° C (59° F and 86° F) [USP].

Manufactured and Distributed by: Bristol-Myers Squibb Company Princeton, NJ 08543-4500

> Comarketed by: Sanofi-Synthelabo Inc. New York, NY 10016

ristol-Myers uibb Company

sanofi~synthelabo

101A5

Revised February 2001

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** NDA 20-757-/S-014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

E, FROMM

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS Clinical Review



NDA:

20-757

Sponsor:

Bristol-Myers Squibb

Submission: SE5-014 (16 February 2000): pharmacokinetic data for irbesartan in children, submitted in partial fulfillment of a Written Request for Pediatric Studies.

Review date: February 28, 2000

REVIEWERS CONCURON

PAUTISES CHANTES TO

--- 10/0/00

Reviewer:

N. Stockbridge, M.D., Ph.D., HFD-110

\_\_\_\_\_

Summary:

This is a review of Study CV131-076, an open-label, single- and multiple-

dose PK study in 23 children age 1 to 17..

Distribution: NDA 20-757

HFD-110/Project Manager

HFD-110/Stockbridge

### Table of contents

I CVI3I-U/6: Pharmacokinetics of irbesarian in hypertensive children and adolescents	
1.1 Source documents	
1.1.1 Investigators	
1.1.2 Study dates	2
1.2 Study design	
1.3 Results	2
1.3.1 Conduct	
1.3.1.1 Effectiveness	3
1.3.1.3 Safety	4
1.4 Summary	4
List of Tables	
Table 1. Demographics (Study CV131-076)	2
List of Figures	
Figure 1. Plasma profiles for first dose by subject (Study CV131-076)	З
Figure 2. Plasma profiles after 2-4 weeks by subject (Study CV131-076)	

# 1 CV131-076: Pharmacokinetics of irbesartan in hypertensive children and adolescents.

### 1.1 Source documents

This review is based upon the amended protocol, dated 3 April 1998, dated amendments, and a final study report dated 22 September 1999 (NDA volumes M18.1-M18.6).

### 1.1.1 Investigators

The study was conducted at 4 US centers.

### 1.1.2 Study dates

Enrollment in the double-blind trial was from 1 June 1997 to 1 February 1999.

### 1.2 Study design

The objective was to obtain pharmacokinetic data from children and adolescents with mild-to-moderate hypertension.

Subjects were males or females age 1 to 16 with seated diastolic pressure at or above the 95<sup>th</sup> percentile for age, gender, and height. Exclusion criteria were (1) clinically significant concomitant disease, (2) renovascular disease or solitary kidney, (3) serum albumin < 2.5 g/dL, (4) clinically significant baseline clinical chemistry abnormalities, (5) history of sensitivity to ACE inhibitors.

Subjects with prior treatment underwent a 1- to 2-week withdrawal phase. Subjects then received irbesartan 2 mg/kg (up to 150 mg) as a single dose, followed by blood sample collection at specified intervals for 72 hours. Subjects received the same dose for 12 to 27 days, followed by 3 days of PK sampling. Nifedipine and HCTZ were allowed to control blood pressure. Planned enrollment was 24.

Study drug 12.5 to 100 mg was encapsulated.

There were no substantive amendments to the protocol.

### 1.3 Results

### 1.3.1 Conduct

A total of 22 subjects were enrolled and 21 subjects completed. One subject (#004/011), a 15-month old male, discontinued after 27 days for an adverse event.

The age, gender, and racial demographic characteristics are shown in Table 1.

Age <sup>2</sup>	Cau	casian	В	Total	
	Male	Female	Male	Female	]
< 1 mo	0	0	0	0	0
1-24 mo	0	0	1	0	1
2-6 y	0	0	0	1	1
6-12 y	1	0	2	5	8
>12 y	2	1	7	3	13
Total	3	1	10	9	23

Table 1. Demographics (Study CV131-076)1.

<sup>&</sup>lt;sup>1</sup> Reviewer analysis of sponsor's dataset demog.xpt.

<sup>&</sup>lt;sup>2</sup> Cut points defined in Written Request letter.

### 1.3.1.1 Effectiveness

Although some blood pressure data were collected, these are difficult to interpret because there was no control group and because of the use of adjunctive therapy.

### 1.3.1.2 Pharmacokinetics

Figure 1 below shows each subject's plasma level of irbesartan as a function of time after the first dose. Plasma levels show no obvious relationship to age when the dosage was adjusted on the basis of body weight.

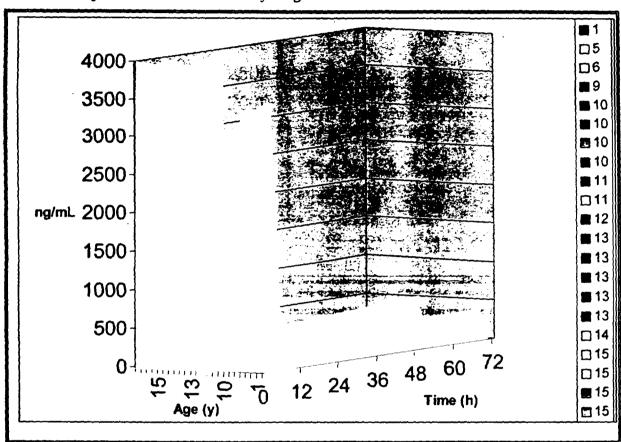


Figure 1. Plasma profiles for first dose by subject (Study CV131-076). Plasma irbesartan levels following the first dose were obtained from dataset CONCN.XPT, and sorted by the age of the subject.

Figure 2 below shows the plasma levels following a dose after 2 or 4 weeks of once-daily administration. There is little accumulation, little or no effect of repeated administration, and no discernible effect of age.

APPEARS THIS WAY
ON ORIGINAL

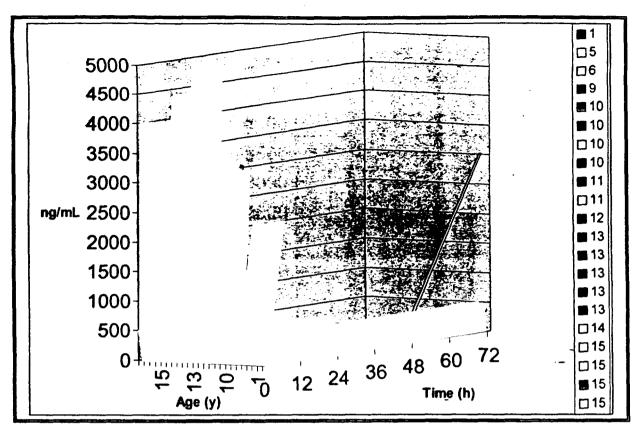


Figure 2. Plasma profiles after 2-4 weeks by subject (Study CV131-076).

Plasma irbesartan levels following repeated dosing were obtained from dataset CONCN.XPT, and sorted by the age of the subject.

-;

## 1.3.1.3 Safety

There were no deaths. There was one serious adverse event—fever and vomiting, leading to discontinuation of a 15-month old subject with sickle cell anemia. Other adverse events and laboratory abnormalities were not serious and not clearly related to treatment.

### -1.4 Summary

See the biopharm review for a more detailed description of the pharmacokinetics. The small number of preschool age subjects should mean that this study does not fulfill the pediatric request's requirements for study of pharmacokinetics.

APPEARS THIS WAY ON ORIGINAL

4

OCT 3 - 2000

# CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW Division of Pharmaceutical Evaluation I

NDA 20-757 Supplement SES-014 SUBMISSION DATE: February 16, 2000

Avapro<sup>R</sup> (75, 150, & 300 mg) Tablets Bristol-Myers Squibb Princeton, NJ

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplemental New Drug Application/Revised Pediatric Labeling

### **SUBMISSION:**

Reference is made to the approved NDA 20-757 for Avapro<sup>R</sup> Tablets, 75, 150, & 300 mg. Avapro (irbersartan) is a nonpeptide, potent, long acting angiotensin II receptor antagonist drug, with high selectivity for the AT<sub>1</sub> subtype receptor. Avapro<sup>R</sup> is an oral agent indicated for the treatment of hypertension.

Supplement SES-014 to NDA 20-757 dated February 16, 2000 includes the results of Study Protocol No. CV131-076 entitled, "Pharmacokinetics of Irbesartan in Hypertensive Children and Adolescents". This Supplement also provides a revised labeling which incorporates the pediatric pharmacokinetic information obtained in the above study.

It should be noted that Study No. CV131-076 does not fulfill the Agency's "Pediatric Exclusivity Written Request" that requires pharmacokinetic data in subjects from four pediatric age groups. However, the sponsor has indicated that additional pharmacokinetic data for infants & toddlers and pre-school children will be submitted in the future in support of the "Pediatric Exclusivity 6-months extension" for Avapro Tablets.

### **RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the Study Report for Protocol No. CV131-076 and the revised version of the labeling for Avapro<sup>R</sup> submitted under NDA 20-757, Supplement SES-014 on February 16, 2000.

Based on the review of the above information, OCPB/DPEI is of the opinion that the pharmacokinetic data provided in the Study Report for Protocol No. CV131-076 are appropriate and can be used to support the pediatric labeling information for school-age children (age >6 to ≤12 years) and adolescents (>12 to ≤16 years). Therefore, from the clinical pharmacology and biopharmaceutic viewpoint the results of the study as well as the labeling revisions are acceptable.

However, it should be noted that the above pharmacokinetic report includes limited safety data and does not include any clinical efficacy information for irbesartan in children. Therefore, the medical reviewer of HFD-110 should determine if the provided data are appropriate to support the pediatric dosing recommendations included in the revised labeling.

Please convey the Recommendation as appropriate to the sponsor.

15/ 10/3/2000

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D.

cc: NDA 20-757, HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

# Attachment I

Includes

NDA 20-757

"Summary of Pharmacokinetic Report:
"Pharmacokinetics of Irbersartan in Hypertensive Children and Adolescents (Protocol No. CV131-076)"

## **Pharmacokinetic Report Summary**

Protocol No.: CV131-076

Study Title: Pharmacokinetics of Irbersartan in Hypertensive Children and Adolescents

### **Principal Investigators:**

- Thomas G. Wells, M.D./Arkansas Children's Hospital, Division of Pediatric Nephrology, Little Rock, AR.
- Alan R. Sinaiko, M.D./University of Minnesota, Dept. Of Pediatrics, Minneapolis, MN.
- Philip D. Walson, M.D./Children's Hospital, Pediatric Clinical Study Center, Columbus, OH.
- Abdullah Sakarcan, M.D./Lousiana State University Medical Center/ Pediatric Nephrology, Shreveport, LA.

### **Objectives:**

- To evaluate the pharmacokinetics of ibersartan in hypertensive children and adolescents.
- To evaluate the antihypertensive response of irbesartan in hypertensive children and adolescents.
- To provide the necessary information for the "Pharmacokinetics; Pediatric" section of the labeling for Avapro Tablets.

<u>Subjects:</u> Twenty-three hypertensive male or non-pregnant female children/adolescents, 1 to 16 years of age with a systolic and/or diastolic blood pressure (BP) ≥ 95th percentile for the child's sex/age/height, were enrolled. Twenty-two completed the study and one was discontinued. The mean demographic characteristics of the children that participated in the study are summarized in Table 1.

TABLE 1

Demographic Characteristics								
	Treatment							
Characteristic	Children < 6 (N = 2)	Children 6-12 y (N = 9)	Adolescents > 12 y (N = 12)					
Age, years Mean (± SD) Range	3 (2.8) I-5	10 (1.7) 6-12	14 (1.3) 13-17a					
Gender, n(%) Male Female	1 (50) 1 (50)	4 (44) 5 (56)	8 (67) 4 (33)					
Race, n(%) White Hispanic/Latino Black	0 0 2(100)	1 (11) 0 8 (89)	3 (25) 0 (0) 9 (75)					
Weight, kg Mean (± SD) Range	20.2(13.9) 10.4-3.0	53.5 (22.98) 22.5-98.6	80.3 (27.41) 35.7-113.4					
Height, cm Mean (± SD) Range	97.8(24.40) 80.5-115	143.5 (12.23) 118-156.5	166.5 (9.74) 147.2-178.0					

Methodology: This was an open label study with Period A and Period B. In Period A, each subject entering the study was to be withdrawn from antihypertensive medications for 7 days. This period may have been extended up to 14 days to allow for washout of antihypertensive medications with a long half-life. A stable dose of nifedipine and/or hydrochlorothiazide (HCTZ) was allowed during Period A, if necessary, to control the subject's hypertension. Also, if necessary nifedipine and/or HCTZ was continued or added during Period B.

Subjects were to fast for 2 hours after each dose, at which time they were to eat a light low-fat breakfast (e.g., 2 slices of toast with jelly and 5 oz of apple juice). Meals on pharmacokinetic sampling days were the same. Subjects received approximately 2 mg/kg irbesartan qd orally for 4 weeks up to a maximum dose of 150 mg qd. This period was abbreviated to 2 weeks if subject participation for 4 weeks was not possible. For dosing, the capsule could be opened and sprinkled on applesauce. For each individual child, the dose was kept constant throughout the study. Pharmacokinetic assessments were performed on Days B1 and B15. Subjects whose blood pressure could not be adequately controlled were to be discontinued. The schedule of events is presented in Table 2.

**TABLE 2. Schedule of Events** 

	SCR	SCR Period A	Peri∞d B			
	Within 14 days	Day Al to A7 (or Al4)	Day Bi	Day B15	Day B29	Discharge
Medical History	Х				İ	
Informed Consent	Х					
Withdraw from Antihypertensive Meds	х					
Pregnancy Test (Serum BHCG)	X	X,				X°
Vital Signs	X	X	X	X	X	Χ°
Physical Examination	X					Χ°
ECG .	<u> </u>					X <sup>6</sup>
Clinical Laboratory Tests	Х					Χ°
Record Concomitant Medication		X	X	X	X	
Dispense Study Medication			Х	X		
Administer Study Medication			X	X		
Study Medication Compliance				X	X	
Serial Blood Sampling for PK			X	Χ <sup>¢</sup>		
Record Adverse Events		X	Х	X	X	
Discharge		X		Χ <sup>ε</sup>	X'	

### CV131-076

Source: Appendix 5.1A

- a Pregnancy test was performed within 72 hrs prior to the start of Period B study medication.
- b These procedures were performed at end of study discharge or if the subject had received study drug and was prematurely terminated for any reason.
- Performed on Day B15 or on any day between Days B15 and B29.
- d If subject did not meet the criteria for entry to Period B at Day A7 or Day A14, then Discharge procedures were followed.
- e If Subject was participating in study for only 2 weeks, PK was followed by discharge procedures.
- If subject was participating in study for 4 weeks, discharge procedures were to be followed then.

### Study Drug:

The following capsules strengths were available: 12.5, 25, 37.5, 50, 75 and 100 mg. The capsule or combination of capsules achieving a dose closest to 2 mg/kg was used. Bristol-Myers Squibb supplied the following study drugs:

DRUG	ORAL DOSE	BATCH NUMBER	APPEARANCE
Irbesartan	12.5 mg	N96021	gray, size 0, opaque capsules
Irbesartan	2.5 mg	N94F095C	gray, size 0, opaque capsules
Irbesartan	37.5 mg	N95154	gray, size 0, opaque capsules
Irbesartan	50 mg	N95024	gray, size 0, opaque capsules
Irbesartan	75 mg	N95067	gray, size 0, opaque capsules
Irbesartan	100 mg	N95147	gray, size 0, opaque capsules
Placebo Matching Irbesartan		N95144	gray, size 0, opaque capsules

### **Prior and Concomitant Therapy:**

All concomitant medications were recorded on the Case Report Form for the appropriate visit. Subjects were required to refrain from taking routine daily medications until after 4 hours after the morning dose of medication. Subjects could not receive any dosage changes in current medications or any new medications (except for nifedipine and HCTZ) for at least 2 weeks before Period A and for the duration of the study. Subjects were to take no additional medication (including herbal medications), food supplements, potassium-containing preparations or vitamin or mineral supplements unless the specific preparation was reviewed by the investigator against the protocol's exclusions and restrictions.

Medications permitted as needed during the study.

HCTZ or nifedipine as per protocol

The following medications were permitted during the study if the daily dose administered during the study remained stable and was not administered for 4 hours before or after the morning dose of study medication:

- Acetaminophen (PRN) in standard doses
- Antacids or stable H2 receptor antagonist therapy (except cimetidine and omeprazole)
- Multivitamins if taken daily
- Insulin
- Inhaled steroids

The following concomitant vasoactive drugs were not permitted during the study:

- Nitrates
- Topical f3-adrenergic blocking agents
- Oral antihistamines

### Medications prohibited were:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and any preparations containing them were not permitted for 2 weeks prior to or at any time during the study.
- Anticonvulsant medications
- Systemic antibiotics during Period B
- Antacid ingestion within 4 hours of study drug, or daytime H2 antagonists
- Cirnetidine or omeprazole
- Oral steroids

- Bile acids binding resins (e.g., cholestyramine, colestipol).
- Diuretics (other than HCTZ), B-blockers, ACE inhibitors, calcium antagonists (other than nifedipine), vasodilators or any other antihypertensive medication
- Digoxir
- Methylphenidate (Ritalin®)

### **Evaluation:**

- Pharmacokinetics: PK of irbesartan in hypertensive children and adolescents was evaluated on Day B1 and then again on Day B15.
- Efficacy: Not applicable.
- Safety: A complete physical examination (including seated vital signs and body weight) and a 12-1ead ECG were performed at screening and prior to study discharge. The antihypertensive response of irbesartan was also evaluated. Seated BP and HR was measured at predose on Days B I and B 15 or later.

<u>Blood Sample Collection for PK:</u> Blood samples (1 mL) were collected immediately prior to dosing (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 h after dosing on Days 1 and 15. However, following an administrative letter to the protocol, the 48 h and 72 h samples after the last dose were not collected for the majority of subjects.

Analytical Methodology: Plasma samples were assayed for irbesartan by a validated The lower limit of quantitation of this method was ng/mL. Quality control (QC) samples prepared at the time of sample analysis were analyzed along with the study samples to assess assay accuracy and precision.

### **Pharmacokinetic Parameters:**

The following parameters for irbesartan were derived from the plasma concentration-time profiles:

CMAX (ng/mL) Maximum observed concentration
TMAX (h) Time at which CMAX was observed

TAUC(0-T) (ng.h/mL) Trapezoidal area under the concentration-time curve from time zero to the time of the last quantifiable

concentration

TAUC(TAU) (ng. h/mL) Trapezoidal area under the concentration-time curve in one dosing interval

CLT/F (L/min) Apparent oral clearance of orally administered doses of irbesartan, calculated as the ratio of dose to

TAUC(0-T) for the single dose on Day 1 or as the ratio of dose to TAUC(0-24h) for the steady state

Al Accumulation index, calculated as the ratio of TAUC(0-24) at steady-state to TAUC(0-24) after the first

dose

### **Statistical Methods:**

Sample Size and Power: A previous study, CV131-004, reported a coefficient of variation (CV%) of 37.9% for AUC(TAU) after 29 days of 100 mg qd dosing of irbesartan to male and female adult subjects with mild to moderate hypertension. Assuming that the CV was similar in this study, the proposed

sample size of 24 subjects would allow approximately 95% confidence that the estimated AUC(TAU) mean would differ from the true population mean by at most 16%; that is, the 95% confidence interval for the mean would be the estimated mean plus or minus approximately 16%.

### **Analysis of PK Data:**

- Summary statistics for the PK parameters were computed by sampling interval for each age group.
- Irbesartan pharmacokinetic parameters and the dose normalized TAUC<sub>o-T</sub> and CMAX were tabulated.
- For the estimation of oral clearance, the truncated AUC of irbesartan from time 0 to the last measurable concentration, TAUC(0-T), was used (due to the fact that the mean plasma concentrations of irbesartan at 24 h in patients ≥ 6 years had declined by more than 90% of the CMAX values, indicating that the terminal phase did not contribute substantially to the AUC extrapolated to infinity nor did it predict the degree of accumulation).

### Analysis of Safety Data:

- Adverse Events (AEs): All adverse events recorded during the study were listed and tabulated by treatment, body system and primary term. Any serious adverse event was identified.
- Laboratory Abnormalities: All abnormalities meeting predefined criteria were listed and tabulated by treatment and laboratory test.
- Laboratory Evaluations: In addition to the tabulation of abnormalities, summary statistics for selected clinical' laboratory test results, seated blood pressure, seated heart rate and ECG measurements, were tabulated by treatment and time point.

### **RESULTS:**

Analytical: The validation results indicate that the performance of the assay fulfilled the requirements for an accurate and precise analytical method. The standard curves were linear ( $R^2 \ge 0.991$ ) over the concentration range of ng/mL. The between-run precision and the within-run precision for analytical QC samples were no greater than and % relative standard deviation (%RSD), respectively, with deviations from the nominal concentrations of less than . %. Summary results for the QC samples are listed in Table 3

TABLE 3 Summary of Quality Control Data for Irbesartan in Plasma

CONCONCENTRATION [NG/ML]	3.00	5.00	100.0	500.0	<b>8</b> 50.0	2000.0	2500.0
N /	22	2	31	34	36	2	10
Mean Obs. Concentration	3.02	4.78	97.53	490.16	842.15	2053.59	2487.01
% of Deviation	0.94	-4.40	-2.46	-1.96	-0.92	2.68	-0.52
Between Run precision (RSD%)	2.68	NA	2.43	0.00	2.41	NA	4.14
Within Run Precision (RSD%)	6.74	NA	4.09	5.18	4.33	NA	3.99

Pharmacokinetics: The mean plasma concentration-time profiles of irbesartan in children and adolescents following single and repeated daily 2 mg/kg oral doses of irbesartan in this study and in adults following a single 150 mg dose (approximately 2mg/kg) are illustrated in Figure 1. The pharmacokinetic parameters of irbesartan by age group following single and repeated daily 2 mg/kg oral doses of irbesartan are summarized in Table 4

FIGURE 1

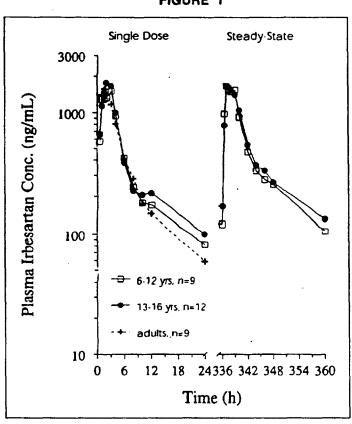


TABLE 4. Summary of Pharmacokinetic Parameters of Irbesartan by Age Group

PHARMACOKINETIC  PARAMETER  [Arithmetic Mean (SD)]	Children 1-23 Months of Age		Children 2-5 Years of Age		Children 6-12 Years of Age		Children 13-16 Years of Age	
	Single (n=1)	Multiple (n=1)	Single (n=1)	Multiple (n=1)	Single (n=9)	Multiple (n=9)	Single (n=12)	Multiple (n=12)
CMAX (ng/mL)	1740	<u> </u>	2931	1092	1751 (613)	2304 (1246)	2157 (973)	2079 (990)
TAUC (ng.h/mL)	3745		11040	5177	8707 (3098)	11408 (4588)	11163 (4685)	11408 (4588
TMAX (h)	1.0		4.0	3.0	1.0-4.0	0.5-4.0	1.5-4.0	0.5-4.0
CLT/F (L/min)	0.11		0.08	0.16	0.2 (0.06)	0.21 (0.12)	0.24 (0.12)	0.23 (0.11)
Al ``	<u> </u>	<u> </u>		0.47	·	1.09	-	1.2
Dose Norm. CMAX (ng/mL/mg)	69.6	<u> </u>	58.6	21.8	17	20.6	14.8	13.9
Dose Norm TAUC (ng.h/mL/mg)	149.8	1	220.8	103.5	85.3	93.7	56.3	79.3

Pharmacodynamics: Plasma concentrations of irbesartan were in general, associated with decreases in SeSBP and/or SeDBP, irrespective of whether the subject was receiving other concomitant antihypertensive medications. In the 12 subjects that did not receive concomitant antihypertensive medication mean decreases in SeSBP/SeDBP were -8/-7 and -16/-10 after 14 and 28 days of dosing with irbesartan, respectively. While the 11 subjects who continued to receive a variety of antihypertensive medications had additional mean decreases in SeSBP/SeDBP of-5/-8 and -5/-4 after 14 and 28 days of dosing with irbesartan, respectively.

Safety: Irbesartan, given up to a I50 mg dose to children and adolescents was well tolerated. There were no deaths in this study. One SAE (fever and vomiting) was reported which led to the discontinuation of the subject from the study. Fourteen (14) treatment-emergent AEs were reported by 9 of the 23 subjects. The most frequently reported AEs were headache and pharyngitis. Fourteen (14) MAs were reported by 12 subjects in this study. Urinary red blood cells was the most frequently reported MA. None of the subjects discontinued from the study because of marked abnormalities.

### **CONCLUSIONS:**

- The overall objective of this study was to characterize the pharmacokinetics and antihypertensive response of irbesartan after oral administration in children and adolescents with hypertension. Twenty-three patients (age ranging from 1.25 years to 16 years) participated in the study. For comparison of the pharmacokinetic parameters, the patients were divided into the following age groups: 1-23 months, 2-5 years, 6-12 years, and 13-16 years. However, only one patient each in the 1-23 months and 2-5 year age groups participated in the study. Hence, the pharmacokinetic parameters of irbesartan obtained in these two age groups were not compared with those in the other groups, and no recommendations for dosing irbesartan to children < 6 years of age are made in this report. A subsequent study is planned for the investigation of pharmacokinetics in children < 6 years of age.</p>
- The pharmacokinetic parameters of irbesartan were comparable between male and female subjects and between the age groups of 6-12 years and 13-16 years.
- Little accumulation of irbesartan (18%) was observed in plasma upon repeated once daily dosing in these subjects.
- In a previous study, the mean CMAX and AUC values of irbesartan following a single 150 mg oral dose in young adults (18-40 years) were 1854 ng/mL and 9715 ng/mL, respectively. Corresponding values at steady state were 2039 ng/mL and 9278 ng/mL, respectively. These values are comparable to those obtained in children of 6-16 years of age following single 2 mg/kg doses. Therefore, a 2 mg/kg dose in pediatric patients results in comparable exposure to that of adults receiving a therapeutic dose (150 mg) dose.
- In general, administration of 2 mg/kg irbesartan to hypertensive children and adolescents was associated with decreases in BP.

- Irbesartan, given up to a 150 mg dose to children and adolescents, was well tolerated. It should be noted that irbesartan has been well tolerated at doses greater than 12 mg/kg (up to 900 mg) in healthy adults.
- The dosing recommended in the labeling for subjects in the age range of 6 years to 16 years was based on the goal of achieving an exposure in children equivalent to that of adults receiving a dose with proven efficacy.
- Although in this study irbesartan was administered on the basis of body weight (i.e., 2 mg/kg), the proposed dosing guidelines are based on administration of unit dosage form(s). For the dosing recommendations the sponsor took into consideration; (a) the established safety profile of irbesartan, (b) the observed irbesartan plasma concentrations, (c) and the fact that hypertensive children and adolescents are likely to be obese, with body weights greater than the 50th percentile values for normal healthy children and adolescents. Based on the above, the sponsor's proposed dosing guidelines are: an initial dose of 75 mg for children of 6-12 years of age and a starting dose of 150 mg for children in the age group of 13-16 years.

### **REVIWER COMMENTS:**

- 1. The pharmacokinetic information and data analysis for irbesartan in children, are appropriate. However, it should be noted that this report does not fulfill the Agency's "Pediatric Exclusivity Request".
- 2. The assay validation and quality control data showed that the accuracy and precision of the assay are appropriate.
- Finally, it should be noted this report includes limited safety data and does not include any clinical
  efficacy information for irbesartan in children. Therefore, the medical reviewer of HFD-110 should
  determine if the provided data are appropriate to support the pediatric dosing recommendations
  included in the revised labeling.
- 4. With respect to the revised labeling, the proposed pediatric information is acceptable provided the following modifications are incorporated into the labelina:

DRAFT LABELING

APPEARS THIS WAY
ON ORIGINAL

# Attachment II

Includes

NDA 20-757

Revised Labeling

7 pages redacted from this section of the approval package consisted of draft labeling

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** NDA 20-757/S-014

## **ADMINISTRATIVE DOCUMENTS**

# DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration

ARRANGEMENTS OF CLINICAL INVESTIGATORS

Food and Drug Administration
CERTIFICATION: FINANCIAL INTERESTS AND

Form Approved: OMB No. 0910-0396

Expiration Date: 3/31/02

#### TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application. I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

gators	Please see attached list.	
Investi		
Clinical		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Thorir D. Bjornsson, M.D., Ph.D.	Vice President, Clinical Pharmacology
FIRM/ORGANIZATION	
Bristol-Myers Squibb	
Viliam D. Bjansk	m 1/25/81

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857 Redacted 2

pages of trade

secret and/or

confidential

commercial

information

## FDA Links Searches Check Lists Tracking Links Calendars Reports Help

## PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

## View as Word Document

**NDA Number:** 

020757

Trade Name:

AVAPRO (IRBESARTAN) TABS 75/150/300 MG

Supplement Number: 014

Generic Name:

IRBESARTAN TABS 75/150/300MG

Supplement Type:

Dosage Form:

Regulatory Action:

ΑE

**COMIS Indication: TREATMENT OF HYPERTENSION** 

Action Date:

12/15/00

Indication # 1

Hypertension

Label Adequacy: Adequate for ALL pediatric age groups

Formulation

NO NEW FORMULATION is needed

Needed:

Comments (if any):

Pediatric changes to the Clinical Pharmacology, Precautions, and Dosage and Administration section in partial

5/11/01

response to our Pediatric Written Request-05/11/01

Ranges for This Indication

0 years

Lower Range

Upper Range

Adult

<u>Status</u> Completed **Date** 

This page was last edited on 5/11/01

Signature

EXCLUSIVITY SUMMARY FOR NDA # 20-757 SUPPL #_SE5-014	
Trade Name: Avapro Generic Name: Irbesartan Tablets	
Applicant Name: Bristol-Myers Squibb Pharmaceutical Institute HFD # 110	
Approval Date If Known:	
PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?	
1. An exclusivity determination will be made for all original applications, but only for consupplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to o more of the following question about the submission.	
a) Is it an original NDA? YES / / NO / X /	

YES	/_X/ NO //	
If ye	es, what type? (SE1, SE2, etc.)	_SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /\_ \_\_/ NO /\_X\_\_/

b) Is it an effectiveness supplement?

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor submitted pharmacokinetic data in partial response to our Pediatric Written Request. The idea was to place some information in the labeling about the pK profile of the drug in children; more data will be forthcoming when the study is completed.

d) Did the applicant request exclusivity?

YES /\_\_/ NO /\_X\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

IF YC	U HAVE	ANSWERE	D "NO"	TO ALI	OF THE	<b>ABOVE</b>	QUESTIONS,	GO	DIRECTLY	TO
THE S	IGNATU	RE BLOCKS	ON PA	GE 8.						

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)
YES /X/ NO //
If yes, NDA # 20-757 Drug Name Avapro (irbesartan) Tablets
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.
3. Is this drug product or indication a DESI upgrade?
YES // NO //
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).
PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)
1. Single active ingredient product.
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.
YES // NO // If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
NDA#
NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)  YES // NO //
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
NDA#
NDA#
NDA#
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.
PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.
YES // NO//
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently

investigation submitted in the application.						
(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?  YES // NO //						
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:						
(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?						
YES /_/ NO/_/  (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.						
YES // NO //						
If yes, explain:						
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?						
YES // NO //						
If yes, explain:						
(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the appropriation that are essential to the approval:						

would have been sufficient to support approval of the application, without reference to the clinical

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.							
the agency to demonstra	te the effectiveness of a p	to the approval," has the investigation been relied on by previously approved drug product? (If the investigation busly approved drug, answer "no.")					
Investigation #1	YES //	NO //					
Investigation #2	YES //	NO //					
If you have answered "you in which each was relied		tigations, identify each such investigation and the NDA					
•	stigation that was relied g product?	to the approval", does the investigation duplicate the on by the agency to support the effectiveness of a					
Investigation #1	YES //	NO //					
Investigation #2	YES //	NO //					
If you have answered investigation was relied		investigation, identify the NDA in which a similar					
c) If the answers to 3( supplement that is essen "new"):	(a) and 3(b) are no, idential to the approval (i.e.,	entify each "new" investigation in the application or the investigations listed in #2(c), less any that are not					

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.						
	fied in response to question 3(c): it ified on the FDA 1571 as the spon	f the investigation was carried out under sor?				
Investigation #1						
IND # YES //	! NO // Explain:					
Investigation #2						
IND #/	NO // Explain:					
		which the applicant was not identified as decessor in interest provided substantial				
Investigation #1						
YES // Explain	NO// Explain					
		-				
Investigation #2						
YES //Explain	NO // Explain	<del>-</del>				
		_				

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES //	NO /	/		
If yes, explain: _				
			<del></del>	<u>,,,_</u>
<b>/</b> S/				
Signature	Date			

Signature of Office/ Division Director

Title:

Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

3. Under DOSAGE and ADMINISTRATION, a Pediatric Patients subsection has been added:

Children (< 6 years): safety and effectiveness have not been established.

Children (6-12 years): An initial dose of 75 mg once daily is recommended. Patients requiring further reduction in blood pressure should be titrated to 150 mg once daily. (see PRECAUTIONS; Pediatric Use).

Adolescent patients (13-16 years): An initial dose of 150 mg once daily is recommended. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see PRECAUTIONS; Pediatric Use).

The Biopharmaceutics reviewer (with the medical officer's concurrence) suggested minor modifications to the CLINICAL PHARMACOLOGY and PRECAUTION sections of the labeling:

1. CLINICAL PHARMACOLOGY, Special Populations, Pediatric subsection should read as follows:

The pharmacokinetics of irbesartan were studied in hypertensive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following single and multiple daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and Cmax values were comparable to adults receiving 150 mg daily. Irbesartan pharmacokinetics have not been investigated in patients <6 years of age.

2. PRECAUTIONS, Pediatric Use subsection should read as follows:

Pharmacokinetic parameters in pediatric patients (age 6-16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (see CLINICAL PHARMACOLOGY; Special Populations). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (See DOSAGE and ADMININSTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

Dr. Lipicky said the above suggestions were acceptable. He said in addition, the statement in the PRECAUTIONS, Pediatric Use subsection, "Safety and effectiveness in pediatric patients have not been established" should not be deleted as the sponsor proposes. The PRECAUTIONS, Pediatric Use subsection should now read as follows:

٠.

Safety and effectiveness in pediatric patients have not been established.

Pharmacokinetic parameters in pediatric patients (age 6-16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (see CLINICAL PHARMACOLOGY; Special Populations). Blood pressure

reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (See DOSAGE and ADMININSTRATION: Pediatric Patients). AVAPRO has not been studied in pediatric patients less than 6 years old.

Comments/Recommendations: An approvable letter will be drafted for Dr. Lipicky's signature.

Edward Fromm

Regulatory Health Project Manager

Ef/12-12-00

cc: NDA 20-757

> HFD-2 HFD-110

HFD-110/EFromm/Blount



Food and Drug Administration Rockville MD 20857

FEB - 4 2000

Four Years from the Date of this Letter FEB 4 2004

IND

Bristol-Myers Squibb Attention: Ms. Mary Ellen Norvitch P.O. Box 4000 Princeton, NJ 08543-4000

Dear Ms. Norvitch:

Reference is made to our December 23, 1998 written request for pediatric studies for Avapro (irbesartan). We have recently reviewed that written request and have decided to amend it. Please note that the following Written Request supercedes that of December 23, 1998, which is no longer valid.

Changes have been made to the following sections:

- 1. The third bullet under "strategy,"
- 2. The fourth and fifth bullet under "age groups,"
- 3. The second sentence under "recruiting,"
- 4. "Format of Reports," and
- 5. The date the reports are due
- 6. Timing of Submission of Reports

## Strategy

The requested data will provide guidance for the use of irbesartan to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial, and an open treatment phase following the trial or other comparable database, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of irbesartan on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

## **Pediatric Subgroups**

#### Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1 24 months),
- pre-school children (age 2 6 years),
- school-age children (age 6 12 years or ≤ Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (> 12 years or > Tanner Stage 3 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school "and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

## Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

#### Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailability compared to the marketed product.

#### Dose-ranging Trial

#### Trial Design

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of irbesartan is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of irbesartan, with the doses chosen to give blood levels in a range from slightly.

less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose.

After two weeks of treatment,<sup>2</sup> the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.<sup>3</sup> If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show not effect), but it would be interpretable.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful. In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of irbesartan and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

#### Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and at least 50% of the patients in the trial should be 6 − 12 years old or ≤ Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with irbesartan or other therapy should be neither required nor disqualifying.

Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

<sup>&</sup>lt;sup>2</sup> The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

## Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

#### Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

#### Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

#### Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to irbesartan and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life,  $C_{max}$ , and  $t_{max}$  in pediatric subjects of the various age groups.

## Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. You may submit this report with essential data in electronic form, with a case report form annotated with the names of the SAS variables used.

#### Labeling Changes

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population<sup>5</sup> that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

<sup>&</sup>lt;sup>5</sup> For example, pediatric patients with hypertension secondary to advanced renal disease.

## Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before <u>four years from the date of this letter</u>. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact:

Mr. Edward Fromm Regulatory Heath Project Manager (301) 594-5313

Sincerely yours,

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

2/4/00